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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/817,318	03/26/2001	Susana Salceda	DEX-0199	1254

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	13

DATE MAILED: 02/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/817,318	SALCEDA ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sh t with th correspondenc address --

Period for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 2, 7, 8, 9 and 10-25.

Accordingly, claims 1, 3-6 are examined in the instant application.

SEQUENCE RULE COMPLIANCE

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821-25 for the following reasons:

The amino acid sequence in the amended claim 1 is not accompanied by a sequence identification number.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Claims 1, 3-6 remain rejected under 35 USC 112, first paragraph, pertaining to lack of a clear written description of a fragment of SEQ ID NO:1 and a nucleic acid

sequence with 95% identity to an antisense sequence of SEQ ID NO:1 for the same reasons already of record in paper No:9.

Applicant amends claim 1 to recite a fragment of SEQ ID NO:1 encoding a 15 to 139 amino acid sequence, and a nucleic acid sequence with 95% identity with an antisense sequence of SEQ ID NO:1. Applicant asserts that said amendments set forth definitive structural feature of the claimed polynucleotides and would obviate the rejection.

Applicant's arguments in paper No: 12 are not persuasive for the following reasons:

It is noted that a fragment of SEQ ID NO:1 encoding a 15 to 139 amino acid sequence encompass unrelated polynucleotide sequences with unknown structure, function and length, provided they share with SEQ ID NO:1 a fragment that encodes a 15 to 139 amino acid sequence.

Further, a nucleic acid sequence with 95% identity to an antisense sequence of SEQ ID NO:1 encompasses variants of SEQ ID NO:1, wherein said variants have 95% sequence identity with SEQ ID NO:1.

The findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly relevant to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of

DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

The specification discloses variants of the claimed polynucleotides, which may result in amino acid substitutions, additions, deletions, fusions and truncations in the polypeptides encoded by said polynucleotides (p.15). The specification also discloses polynucleotides that hybridize to the claimed polynucleotidess, under stringent conditions, in which the sequences have at least 95% or 97% identity between the sequences (p.17). The specification discloses variant polypeptides that have conservative substitutions (p.17, last paragraph bridging p.18). No further description of variants by substitution is provided in the specification.

The claims 1, 3-6 however read on nucleotide sequence variants of SEQ ID NO:1, wherein said variants have any type of substitution besides conservative substitution, at any amino acid, throughout the length of the peptide, as well as insertions and deletions. The specification and the claims do not place any limit on which amino acid to be subjected to conservative or non-conservative substitution, the type of substitution besides conservative substitution, nor the type of amino acids replacing the original amino acids. In addition, the specification and all other pending claims do not place any limit on the number of amino acids that could be substituted. Thus the scope of the claims includes nucleotide sequences encoding numerous

structural variants. Although the specification discloses that the types of changes are routinely done in the art, the specification and the claims do not provide any guidance as to which, or how many original amino acid(s) to be substituted, or to which type of substitution besides conservative substitution, or which amino acids could be deleted or inserted so that the claimed polypeptide could function as contemplated. No common structural attributes that identify the claimed nucleotide sequences encoding said variants are disclosed. In addition, no common functional attributes that identify the claimed nucleotide sequences encoding said variants are disclosed, because the function of a nucleotide sequence could be abolished, even with substitution of only one amino acid of the peptide encoded by said nucleotide sequence (Burgess et al. Journal of Cell Biology, 1990, 11: 2129-2138). The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed nucleotide sequence variants, SEQ ID NO:1 alone is insufficient to describe nucleotide sequence variants. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number nucleotide sequence variants. Thus, applicant was not in possession of the claimed nucleotide sequence variants.

Thus, there is insufficient support of claims 1, 3-6 as provided by the Interim Written Description Guidelines published in the June 5, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645. Therefore, only the nucleic acid

sequence of SEQ ID NO:1, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Claims 1, 3-6 remain rejected under 35 USC 112, first paragraph, pertaining to lack of enablement for a fragment of SEQ ID NO:1 "encoding" a 15 to 139 amino acid sequence for the same reasons already of record in paper No:9.

Applicant asserts that the claims have been amended and no longer include any reference to nucleic acid sequence which encodes a protein.

Applicant's arguments in paper No: 12 are not persuasive for the following reasons:

Claim 1 has been amended to recite for a fragment of SEQ ID NO:1 "encoding" a 15 to 139 amino acid sequence. The claims as written encompass a fragment of SEQ ID NO:1 which is translated *in vivo* into a 15 to 139 amino acid sequence. Since expression of mRNA does not dictate nor predict the translation of such mRNA into a polypeptide, as overwhelmingly taught by Alberts et al, Shantz et al, McClean et al, Fu et al, Yokota et al, all of record, one cannot predict if a fragment of SEQ ID NO:1 is translated *in vivo* into a 15 to 139 amino acid sequence, or even if translated, whether the amino acid sequence is overexpressed.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE, NEW REJECTION

Claims 1, 3-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the nucleic acid sequence of SEQ ID NO:1, does not reasonably provide enablement for a nucleotide sequence with 95% identity to SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Claims 1, 3-4 are drawn to a nucleic acid sequence with 95% identity to an antisense sequence of SEQ ID NO:1, a vector comprising said nucleic acid sequence and a host cell expressing said vector.

It is noted that a nucleic acid sequence with 95% identity to an antisense sequence of SEQ ID NO:1 encompasses variants of SEQ ID NO:1, wherein said variants have 95% sequence identity with SEQ ID NO:1.

The scope of the claims includes numerous structural variants. Applicants have not shown how to make and use the claimed nucleic sequence variants which are capable of functioning as that which is being disclosed.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. Such unpredictability would equally apply to DNA sequences which encode proteins. For example, replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al. Journal of Cell Biology, 1990, 11: 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity

while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252). Similarly, it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (see Tao. et al. The Journal of Immunology, 1989, 143(8): 2595-2601, and Gillies et al. Human Antibodies and Hybridomas, 1990, 1(1): 47-54). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

In view of the above unpredictability, one of skill in the art would be forced into undue experimentation in order to perform the claimed invention as broadly as claimed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

February 3, 2003

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600